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Spinal and Bulbar Muscular Atrophy

[*Kennedy's Disease, SBMA, X-Linked Spinal and Bulbar Muscular Atrophy*]

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Summary

Disease characteristics. Spinal and bulbar muscular atrophy (SBMA) is a gradually progressive neuromuscular disorder in which degeneration of lower motor neurons results in proximal muscle weakness, muscle atrophy, and fasciculations. SBMA occurs only in males. Affected individuals often show gynecomastia, testicular atrophy, and reduced fertility as a result of mild androgen insensitivity.

Diagnosis/testing. All males with SBMA have expansion of a CAG trinucleotide repeat (>35 CAGs) in the androgen receptor *(AR)* gene. Molecular genetic testing for the CAG trinucleotide repeat expansion is available on a clinical basis.

Management. *Treatment of manifestations:* use of braces and walkers for ambulation as needed as the disease progresses; breast reduction surgery for gynecomastia as needed. *Surveillance:* annual assessment of strength; annual assessment of pulmonary function in advanced cases. *Other:* Administration of testosterone and its analogues does not overcome the androgen insensitivity.

Genetic counseling. SBMA is inherited in an X-linked manner. Affected males who are fertile pass the disease-causing allele to each daughter. Carrier females have a 50% chance of transmitting the CAG trinucleotide repeat expansion to each child; males who inherit the mutation will be affected; females who inherit the mutation will be carriers and will usually not be affected. Prenatal testing is available for pregnancies at risk.

Diagnosis

Clinical Diagnosis

The clinical diagnosis of spinal and bulbar muscular atrophy (SBMA) is suspected in males with the following:

- Adolescent-onset signs of androgen insensitivity including gynecomastia and/or small testes with oligospermia or azoospermia
- Post-adolescent onset of
  - Spinal lower motor neuron disease with proximal muscle weakness of the limbs or muscle cramps
  - Bulbar lower motor neuron disease with fasciculations of the tongue, lips, or perioral region; dysarthria and difficulty swallowing
- No signs of upper motor neuron disease such as hyperreflexia or spasticity

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- Family history consistent with X-linked inheritance

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *AR*, the gene encoding the androgen receptor, is the only gene currently known to be associated with SBMA.

Allele sizes. All individuals with SBMA have expansion of a CAG trinucleotide repeat in exon 1 of the *AR* gene.

- **Normal alleles:** 34 or fewer CAG repeats
- **Mutable normal alleles:** None reported to date
- **Reduced penetrance alleles:**Kuhlenbaumer et al (2001) suggest that an allele of 37 CAG repeats can manifest reduced penetrance. Therefore, the clinical significance of alleles with 36-37 CAG repeats should be interpreted within the context of family history, proband/consultand's clinical presentation, and genotype-phenotype correlations in other family members.
- **Full penetrance alleles:** 38 or more CAG repeats
- **Alleles of questionable significance:** There is no consensus as to the clinical significance of alleles of 35 CAG repeats. Interpretation of alleles of this size may require consideration of the affected individual's clinical presentation and reconciliation with repeat sizes in family members.

Clinical uses

- Diagnostic testing
- Carrier testing
- Prenatal diagnosis
- Preimplantation genetic diagnosis

Clinical testing

- **Targeted mutation analysis.** CAG repeat number can be determined by polymerase chain reaction (PCR) amplification of the CAG repeat region within the *AR* gene.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Spinal and Bulbar Muscular Atrophy

Test Method	Mutation Detected	Mutation Detection Rate	Test Availability
Targeted mutation analysis (repeat expansion analysis)	CAG repeat expansion in exon 1 of the *AR* gene	100%	Clinical Testing

Genetically Related (Allelic) Disorders

Mutations in the *AR* gene cause the androgen insensitivity syndrome.

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Clinical Description

Natural History

Spinal and bulbar muscular atrophy (SBMA, or Kennedy's disease, named for the neurologist who originally recognized it) is a disorder of slowly progressive muscle weakness associated with mild androgen insensitivity [Kennedy et al 1968, Harding et al 1982]. Only males are affected.

Neurologic findings. Neurologic symptoms typically begin between age 20 and 50 years [Atsuta et al 2006]. Onset of neurologic symptoms does not occur in childhood or adolescence.

Early signs are difficulty with walking and a tendency to fall. Some individuals have muscle cramps, while others complain of an action tremor [Nagashima et al 1988]. Deep tendon reflexes are decreased.

After one to two decades of symptoms, most affected individuals have difficulty climbing stairs. With time, atrophy of the proximal musculature becomes evident. About one-third of affected individuals require a wheelchair 20 years after the onset of symptoms.

Most individuals eventually show involvement of the bulbar muscles and have difficulty with speech articulation and swallowing. Severely affected individuals (many of whom are non-ambulatory) are at risk for asphyxiation or aspiration pneumonia because of weakness of the bulbar musculature [Kennedy et al 1968, Atsuta et al 2006]. This complication is the only life-threatening problem in SBMA, and probably only becomes important for about 10% of elderly individuals. Therefore, the vast majority of individuals with SBMA have a normal life expectancy and do not die from direct complications of their motor neuron disease. Fifteen of 223 in the Atsuta et al (2006) study died at the mean age of 65.

Some affected males also experience degeneration of the dorsal root ganglia, leading to mild abnormalities in sensory function in the distal extremities [Sobue et al 1981, Nagashima et al 1988, Antonini et al 2000].

Electrodiagnostic studies are consistent with diffuse denervation atrophy, anterior horn cell loss, and sensory neuronopathy [Olney et al 1991, Ferrante & Wilbourn 1997].

Neuropathology. Degeneration of anterior horn cells in the spinal cord of affected individuals is observed [Kennedy et al 1968, Amato et al 1993, Ogata et al 1994]. Immunohistochemistry shows widespread accumulation of mutant androgen receptor (AR) protein [Adachi et al 2005].

Androgen insensitivity. Symptoms of androgen insensitivity typically begin in adolescence with gynecomastia, which is observed frequently in affected males [Warner et al 1992, Sinnreich et al 2004]. Variability in disease severity and progression occurs, both within and between families [La Spada et al 1992, Doyu et al 1993, Lee et al 2005]. This is especially true of the androgen insensitivity signs of testicular atrophy and oligospermia/azoospermia with reduced fertility (see Androgen Insensitivity Syndrome). Many males with SBMA are not able to grow a thick beard and claim that they have had difficulty conceiving.

The androgen insensitivity can be more bothersome to affected individuals than the motor neuron disease, especially early in the course of the disorder [Warner et al 1992].

Heterozygotes —Neurologic findings. Although females who are carriers of an abnormal CAG expansion in the *AR* gene are usually asymptomatic, a number of carriers have experienced muscle cramps or occasional tremors [Nance 1997, Mariotti et al 2000].

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Females who are symptomatic may have an abnormal electromyogram [Sobue et al 1993].

Androgen insensitivity. SBMA is believed to be a sex-limited disease. This means that since females have low levels of circulating androgens, even heterozygotes with a proportion of active mutant alleles are unlikely to be symptomatic.

Genotype-Phenotype Correlations

Studies of CAG repeat length in males with SBMA have established a correlation between expansion size and disease severity. In general CAG repeat length inversely correlates with the age of onset of muscle weakness, difficulty climbing stairs, and wheelchair dependence [La Spada et al 1992]. Thus, males with SBMA with longer CAG repeat expansions tend to have earlier disease onset and more rapid progression [Doyu et al 1992, Igarashi et al 1992]. For example, early onset (age 8-15 years) and rapid progression have been described in a family with 50-54 CAG repeats [Echaniz-Laguna et al 2005].

However, these correlations are only generalizations and exceptions have been reported. For example, a male from a family with SBMA with 37 CAG repeats (the average number of repeats in affected males) has been reported to be asymptomatic at age 46 years [Kuhlenbaumer et al 2001].

The genotype-phenotype correlation between expansion size and disease severity can only account for about 60% of the variability observed in clinical findings, indicating that other factors in addition to CAG repeat length determine disease onset and progression. Indeed, relatives with SBMA with identical CAG repeat lengths may have considerably different disease courses.

Nomenclature

In the past, SBMA has been called X-linked spinal muscular atrophy.

Prevalence

SBMA occurs in fewer than 1:50,000 live male births. It occurs in individuals of Caucasian or Asian racial background but has yet to be reported in individuals of African or aboriginal racial background.

Caucasian ethnic groups in which SBMA has been observed include English, Belgian, French, Italian, German, Polish, Spanish, Swiss, Moroccan, and Turkish [La Spada et al 1991]. A founder effect has been reported in the Scandinavian population [Lund et al 2000].

Asian ethnic groups in which SBMA has been observed include Chinese, Japanese, Korean, and Vietnamese. SBMA appears to be much more common in the Japanese population than in any other ethnic group because of a founder effect [Tanaka et al 1996].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

A number of hereditary and acquired neuromuscular disorders can produce gradually progressive muscle weakness.

The disorder with which spinal and bulbar muscular atrophy (SBMA) is most often confused is amyotrophic lateral sclerosis (ALS). Probably about one in 25 individuals with SBMA are misdiagnosed as having ALS [Parboosingh et al 1997]. Differentiation of ALS from SBMA

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can usually be made based upon history and physical examination. ALS involves upper as well as lower motor neurons; individuals with ALS usually display upper motor neuron signs such as hyperreflexia and spasticity. Individuals with ALS typically show involvement of a wider range of muscle groups as well as a more rapid disease progression. An important feature of SBMA is androgen insensitivity, which often causes gynecomastia; thus evaluation of males with motor neuron disease should include an assessment of breast size to determine if gynecomastia is present [Nagashima et al 1988].

Other forms of spinal muscular atrophy (SMA) that show autosomal recessive, autosomal dominant, and even X-linked inheritance have been described [Zerres 1989]. Of these, autosomal recessive SMA is the most common, occurring as four different phenotypes according to age of onset. Types I-III are known respectively as Werdnig-Hoffman disease (acute), Werdnig-Hoffman disease (chronic), and Kugelberg-Welander disease; all three types present in infancy or childhood, allowing clear differentiation from SBMA. Type IV SMA, like SBMA, shows adult onset [Trentin et al 2005].

Muscle atrophy and muscle weakness from loss of motor neurons in the spinal cord are seen as a part of other inherited neurodegenerative disorders such as spinocerebellar ataxia type 3 (SCA3 or Machado-Joseph disease), Friedreich ataxia (FRDA), Tay-Sachs disease, and the adrenomyeloneuropathy (AMN) variant of X-linked adrenoleukodystrophy (XALD). Individuals with prominent sensory findings in addition to muscle weakness could have a peripheral neuropathy (see Charcot-Marie-Tooth Hereditary Neuropathy Overview).

Non-genetic causes for motor neuron disease include structural lesions (such as spinal cord arterio-venous malformations), infections (especially poliomyelitis), toxins (chronic lead poisoning), metabolic problems (thyrotoxicosis), and paraneoplastic syndromes.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Neurologic assessment with attention to distal muscle strength and deep tendon reflexes
- Assessment of speech
- Assessment of swallowing
- Assessment of androgen responsiveness: male pattern hair growth, testicular size and fertility
- Assessment for gynecomastia

Treatment of Manifestations

Physical therapy and rehabilitation approaches, including the use of braces and walkers, offer the best prospect for remaining ambulatory as the disease progresses.

Some individuals with SBMA have breast reduction surgery for gynecomastia [Sperfeld et al 2002].

Surveillance

- Strength testing (annually)
- Pulmonary function tests (annually in advanced cases)

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Therapies Under Investigation

There is no consensus or clear evidence as to whether androgen or anti-androgen therapy could be an effective form of treatment for the neurologic complications.

- At least one clinical trial has been undertaken, but no significant benefit was derived for the androgen treatment group [Goldenberg & Bradley 1996].
- Anti-androgen therapy seems more promising given what is known about the molecular basis of SBMA. It is widely believed that anti-androgen therapies, even if effective, would need to be administered prior to or early on in the neurodegenerative process. More importantly, the side effects of anti-androgen therapies would probably far outweigh the therapeutic benefit.

Recent studies of amyotrophic lateral sclerosis (ALS) suggest that creatine supplementation may temporarily enhance muscle strength and exercise performance in this motor neuron disease [Mazzini et al 2001], prompting speculation that it may offer a similar benefit to individuals with SBMA.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Administration of male hormones (testosterone and its analogues) is not effective in overcoming the androgen insensitivity.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Spinal and bulbar muscular atrophy (SBMA) is inherited in an X-linked recessive manner.

Risk to Family Members

Parents of a male proband

- The father of a male proband is not affected, nor is he a carrier.
- To date, all mothers of men with SBMA who have been tested have been shown to carry the CAG expansion. However, SBMA is a late-onset disorder and mothers may not always be available for testing.

- The true incidence of *de novo* mutations in men with SBMA is not presently known; no *de novo* mutations have been observed.

Sibs of a proband

- Based on the observation that all tested mothers of affected males are carriers, the chance of transmitting the expanded allele in each pregnancy is 50%.
- Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and will usually not be affected.

Offspring of a proband. All daughters of affected males are obligate carriers. None of the sons are affected.

Other family members of a proband. The proband's maternal aunts may be at risk of being carriers and the aunt's offspring, depending upon their gender, may be at risk of being carriers or of being affected.

Carrier Detection

Carrier testing of at-risk female relatives is clinically available.

Related Genetic Counseling Issues

CAG repeat expansion instability. CAG repeat expansions that cause disease in SBMA have the property of genetic instability, meaning that they often change length when transmitted from parent to offspring. In SBMA, a slight tendency toward CAG repeat expansion exists, although the CAG repeat size is relatively stable with only small repeat length shifts and frequent small contractions. Repeat instability with male transmission of the expanded allele has been described. Although a correlation exists between CAG repeat length and disease onset and severity in individuals with SBMA, prediction of disease course **cannot** be based on measured CAG repeat length.

Testing of at-risk asymptomatic individuals during childhood. Consensus holds that individuals younger than age 18 years who are at risk for adult-onset disorders should not have testing in the absence of symptoms. The principal arguments against testing asymptomatic individuals during childhood are that it removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications. Children who are asymptomatic usually benefit from having a specific diagnosis established.

See also the National Society of Genetic Counselors resolution on genetic testing of children and American Society of Human Genetics and American College of Medical Genetics (1995) Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents.

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See DNA Banking for a list of laboratories offering this service.

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Prenatal Testing

Prenatal testing is possible for pregnancies of women who are carriers if the CAG repeat expansion has been identified in a family member. The usual procedure is to determine the sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at about ten to 12 weeks' gestation or by amniocentesis usually performed at about 15-18 weeks' gestation. If the karyotype is 46,XY, DNA from fetal cells can be analyzed for the CAG repeat expansion.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for adult-onset conditions such as SBMA that do not affect intellect or life span are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Spinal and Bulbar Muscular Atrophy

Gene Symbol	Chromosomal Locus	Protein Name
AR	Xq11-q12	Androgen receptor

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Spinal and Bulbar Muscular Atrophy

313200	SPINAL AND BULBAR MUSCULAR ATROPHY, X-LINKED 1; SMAX1
313700	ANDROGEN RECEPTOR; AR

Table C. Genomic Databases for Spinal and Bulbar Muscular Atrophy

Gene Symbol	Locus Specific	Entrez Gene	HGMD
AR	AR	367 (MIM No. 313700)	AR

For a description of the genomic databases listed, click here.

Normal allelic variants: The *AR* gene contains eight exons and spans 80-100 kb [Brown et al 1989]. A highly polymorphic CAG repeat starting at amino acid codon number 58 is found within the *AR* coding domain. Normal individuals have nine to 34 CAG triplet repeats. About 98% of females show different *AR* CAG repeat lengths on their two X chromosomes, making the *AR* CAG repeat a useful marker for studying X-chromosome inactivation. The most common alleles number from 18 to 25 CAG repeats. Variation in mean CAG repeat length occurs within different racial populations, with Africans having the smallest mean CAG repeat length and Asians having the largest mean CAG repeat length — the CAG repeat length in

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Caucasians being intermediate to these two. Epidemiologic evidence showing that shorter CAG repeat lengths correlate with more aggressive prostate cancers in males has been presented.

Pathologic allelic variants: Expansion of a variable CAG trinucleotide repeat within the coding region of the *AR* gene was found to be absolutely associated with the spinal bulbar muscular atrophy (SBMA) phenotype [La Spada et al 1991].

Genetic testing of sperm for a person affected with SBMA has shown that 20% of the cells had a CAG repeat number equal to the DNA from somatic cells, whereas 56% of the cells contained further expansion of the CAG repeat number, and 24% of the cells contained contraction of the CAG repeat number. Most of the expansions and contractions were between one and three CAG repeats. These results contrast with sperm analysis findings in individuals with Huntington disease in whom greater instability of CAG repeat number is observed [Grewal et al 1998].

Normal gene product: The *AR* gene is a member of the steroid receptor superfamily and therefore displays a typical protein structure, consisting of a highly conserved DNA-binding domain at the center of the protein and a highly conserved ligand-binding domain at the C-terminal end. The *AR* cDNA is 2.8 kb in length and normally encodes a 919-amino acid protein with molecular mass of approximately 110 kd. A second isoform of approximately 87 kd is found in most cell types and likely reflects translation initiation at methionine 188 [Gao & McPhaul 1998]. The N-terminal region of the androgen receptor (AR) protein is relatively poorly conserved and is thought to mediate transcriptional activation of target genes [Zhou et al 1995]. The AR protein contains a nuclear localization signal (NLS) at amino acids 627-658.

Abnormal gene product: Individuals with SBMA produce an AR protein that contains a polyglutamine tail at the N-terminal end [La Spada et al 1991]. This polyglutamine tail presumably alters the conformation of the AR protein (or an N-terminal peptide fragment from the AR protein) to produce neurodegeneration in SBMA. The AR protein is expressed in the brain, spinal cord, and muscle [Matsuura et al 1993, Ogata et al 1994].

In all the CAG trinucleotide repeat diseases involving the central nervous system, the CAGs encode the amino acid glutamine [La Spada et al 1994]. These so-called "polyglutamine tract expansion diseases" all produce unrelated proteins, without obvious similarities in function or subcellular localization. How polyglutamine tract expansion leads to neurodegeneration in SBMA and these other diseases is still unknown [Buchanan et al 2004, Beitel et al 2005]. Recent research advances suggest that the polyglutamine tract region is proteolytically processed and a polyglutamine-containing peptide fragment is retained in the nucleus, where it forms neuronal intranuclear inclusions (NIIs). Once in the nucleus, polyglutamine-expanded AR peptide fragments may cause pathology by interfering with transcriptional co-activators such as the CREB-binding protein [McCampbell et al 2000]. NIIs have been found in spinal cord sections from deceased individuals with SBMA [Li et al 1998].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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www.kennedysdisease.org

National Library of Medicine Genetics Home Reference
Spinal and bulbar muscular atrophy

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson AZ 85718-3208
Phone: 800-FIGHT-MD (800-344-4863); 520-529-2000
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

American Society of Human Genetics and American College of Medical Genetics (1995) Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents

National Society of Genetic Counselors (1995) Resolution on prenatal and childhood testing for adult-onset disorders

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Suggested Readings

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Chapter Notes

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